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DOI:
10.1017/S0033291717000058

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Citation for published version (APA):
O'Donoghue, S., Kilmartin, L., O'Hora, D., Emsell, L., Langan, C., McInerney, S., Forde, N. J., Leemans, A., Jeurissen, B., Barker, G. J., McCarthy, P., Cannon, D. M., & McDonald, C. (2017). Anatomical integration and rich-club connectivity in euthymic bipolar disorder. *Psychological Medicine*, *47*(9), 1609-1623. https://doi.org/10.1017/S0033291717000058

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Anatomical Integration and Rich-Club Connectivity in Euthymic Bipolar Disorder

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Number of Pages: 33
Figures: 4, Tables: 3
Abstract Word Count: 244
Total Word Count: 4, 599

Abstract

Background: Although repeatedly associated with white matter microstructural alterations, Bipolar Disorder (BD) has been relatively unexplored using complex network analysis. This method combines structural and diffusion magnetic resonance imaging (MRI) to model the brain as a network and evaluate its topological properties. A group of highly inter-connected high density structures, termed the 'rich-club', represents an important network for integration of brain functioning. This study aimed to assess structural and rich-club connectivity properties in BD through graph theory analyses.

Methods: We obtained structural and diffusion MRI scans from 42 euthymic patients with bipolar 1 disorder and 43 age and gender matched healthy volunteers. Weighted fractional anisotropy (FA) connections mapped between cortical and subcortical structures defined the neuroanatomical networks. Next, we examined between-group differences in features of graph properties and sub-networks.

Results: Patients exhibited significantly reduced clustering coefficient and global efficiency, compared with controls globally and regionally in frontal and occipital regions. Additionally, patients displayed weaker sub-network connectivity in distributed regions. Rich-club analysis revealed subtly reduced density in patients, which did not withstand multiple comparison correction. However, hub identification in most participants indicated differentially affected rich-club membership in the bipolar group, with 2 hubs absent when compared with controls, namely the superior frontal gyrus and thalamus.

Conclusions: This graph theory analysis presents a thorough investigation of topological features of connectivity in euthymic BD. Abnormalities of global and local measures and network components provide further neuroanatomically specific evidence for distributed dysconnectivity as a trait feature of BD.

Introduction

Evidence for white matter disruption from diffusion tensor imaging(DTI) and for dysconnectivity from functional magnetic resonance imaging(fMRI) suggest impaired neuronal connectivity as a potential core feature of bipolar disorder(BD)(Wessa et al. 2014; Kumar et al. 2014; Skudlarski et al. 2013; Emsell & McDonald 2009; Nortje et al. 2013; Vederine et al. 2011; Houenou et al. 2012; Strakowski et al. 2005; Vargas et al. 2013; Strakowski et al. 2012). Advanced diffusion MRI analysis techniques examine the brain *in vivo* to define parameters of neuroanatomical connectivity. Impaired structural connectivity can be assessed on a network scale using graph theory properties(Sporns et al. 2000). BD has been relatively unexplored using complex network analysis, however methodological advances in such neuroimaging analytical techniques can extend local abnormalities beyond the current state-of-the-art approaches to better understand complex behaviors(Bullmore & Sporns 2009; Sporns 2013).

Complex network analysis combines structural and diffusion magnetic resonance imaging (MRI) to model the brain as a neuroanatomical network and evaluate topological organization and properties of brain structure. A network at the macro-scale comprises cortical and subcortical structures represented by “nodes”, and white matter connections, represented by “edges”(Rubinov & Sporns 2010; Sporns 2012; Bullmore & Sporns 2009). Following network construction, graph theory properties characterize brain integration and segregation(Bullmore & Sporns 2009; Rubinov & Sporns 2010; Bullmore & Sporns 2012). These properties include global measures quantifying whole brain integration and connectedness, and local measures to characterize segregation: how cortical and subcortical structures cluster into communities and the anatomical architecture of their connections with nearby regions(Bassett et al. 2011;

Bullmore & Sporns 2009). Therefore, graph analysis extends DTI analysis of microstructural white matter to characterize patterns of organization.

Recently, neuroimaging studies applied graph properties across a range of brain disorders, including autism, amyotrophic lateral sclerosis, Alzheimer's disease, multiple sclerosis and schizophrenia(Crossley et al. 2014; Griffa et al. 2013; Fornito, Harrison, et al. 2013; Fornito et al. 2015), with few network investigations in BD(Leow et al. 2012; Gadelkarim et al. 2014; Forde et al. 2015; Ajilore et al. 2015; Collin et al. 2015).

Assessment of neuroanatomical sub-networks, connectivity between several brain regions, assumes connections belonging to the same component are highly connected(Meskaldji et al. 2011; Zalesky et al. 2010). The Network Based Statistic tests for connectivity effects in edge weights within sub-networks. Therefore, investigation of sub-networks may identify regionally specific structural dysconnectivity in BD.

Furthermore, key hubs with major interconnections, termed the rich-club, appear to play a key role integrating brain functioning and may be impaired in brain disorders(van den Heuvel & Sporns 2011; Crossley et al. 2014; Collin et al. 2013; Crossley et al. 2013; Sporns & Van Den Heuvel 2013). Hubs, or nodes that are highly connected, appear to be involved in executive function, the salience network and the default mode network when the mind is at rest(van den Heuvel & Sporns 2011; Crossley et al. 2013; Senden et al. 2014). Rich-club structures identified in healthy human brain networks includes regions previously implicated in mood regulation and BD, for example the hippocampus, striatum and thalamus(Hallahan et al. 2011; Houenou et al. 2012) and their connections(Emsell, Leemans, et al. 2013; Emsell, Langan, et al. 2013; Nortje et al. 2013; Ellison-Wright et al. 2014).

Previously, we demonstrated FA reductions in the corpus callosum and limbic pathways (Emsell, Leemans, et al. 2013) consistent with other DTI studies(Vederine et al. 2011; Nortje et al. 2013). Therefore, we sought to further examine regional connections defined by nodes connecting the corpus callosum and cingulum(Emsell, Langan, et al. 2013). The present study aimed to investigate dysconnectivity in BD through global, local, network component and rich-club connectivity measures in a large clinically homogenous sample of patients with euthymic BD.

Methods

Participants

Thirty-five participants between 18 and 60 years of age were recruited from the local community as part of the Galway Bipolar Study(Emsell, Leemans, et al. 2013; Emsell, Langan, et al. 2013). An additional seven individuals with remitted BD participated in a follow-up imaging of a first episode psychosis study and underwent an identical scanning procedure were included in connectivity analysis(Scanlon et al. 2014; Kenney et al. 2015). We recruited 43 age and gender matched healthy volunteers from the local community. Forty-two patients with BD type 1 was confirmed using the DSM-IV Structured Clinical Interview for DSM Disorders(APA 1994). Exclusion criteria for all participants included a history of medical or neurological illness, history of head injury resulting in loss of consciousness for over 5 minutes, history of substance abuse in the past year, learning disability, and oral steroid use in previous 3 months. Further exclusion criteria for controls included personal or family history of psychotic or affective disorder in first or second-degree relatives. Additional patient exclusion criteria included a lifetime comorbid DSM-IV Axis 1 disorder. All patients were euthymic at the time of scanning, defined as a score

<7 on both the Hamilton Rating Scale for Depression and Young Mania Rating Scale(Hamilton 1960; Young et al. 1978). Ethical approval was obtained from the National University of Ireland Galway and University Hospital Galway research ethics committees. After a complete description of the study was presented to participants, written informed consent was obtained.

MRI Acquisition

All participants were scanned with identical imaging acquisition parameters. Structural MRI data was acquired on a 1.5 Tesla Siemens Magneto Symphony Scanner using a 4-channel head coil. Volumetric T1-weighted magnetization prepared acquisition of gradient echo (MPRAGE) sequence acquired with imaging parameters repetition time(TR): 1140 ms, echo time(TE): 4.38ms, inversion time(TI): 600 ms, flip angle 15; matrix size 256x256; an in-plane pixel size 0.9x0.9 mm^2; slice thickness of 0.9 mm.

Diffusion MRI data was acquired using an 8-channel head coil with an echo planar image diffusion sequence acquired with parallel imaging, 64 optimized diffusion gradient directions with b=1300 s/mm^2, 7 non-diffusion weighted images, repetition time=8100 ms, echo time=95 ms, field of view = 240 x 240 mm^2, matrix = 96 x 96, in-plane voxel size of 2.5x2.5 mm^2, slice thickness=2.5 mm, 60 slices.

Pre-processing

All MR images were corrected for subject motion and eddy current distortions using the dMRI analysis software toolbox *ExploreDTI* v.4.8.3(Leemans et al. 2009). The b-matrix was rotated to preserve diffusion orientation information within voxels during subject motion correction(Leemans & Jones 2009). Quality assessment for all diffusion MR images examined scans for potential artifacts including hypointensities, shift in images, and signal dropout. We

rated MR images on a quality scale from mild to severe. Participants with poor MR image quality were excluded from subsequent analyses.

Whole Brain Tractography

Whole brain white matter tractography reconstructed the series of streamlines used to define the "edges" in complex network analysis. White matter pathways were reconstructed using *ExploreDTI* v.4.8.3(Leemans et al. 2009). Robust estimation of the diffusion tensor was implemented using the RESTORE approach(Chang et al. 2005). A deterministic constrained spherical deconvolution algorithm accounted for crossing fibers present within voxels(Tournier et al. 2007; Jeurissen et al. 2011). Fiber tracking initiated in each voxel and continued with a step size of 1 mm until the following threshold was exceeded: fiber orientation distribution >.15, angle threshold curvature >30◦, minimum length <20 mm, and maximum length > 300 mm. A spherical harmonic order of L_{max}=8 was applied.

Generating Connectivity Matrices

The series of tractography streamlines are mapped through cortical and subcortical structures to produce a weighted and undirected 90x90 connectivity matrix for each subject. Connectome maps did not correct for changes in ROI structural volume. Visual inspection using MRIcron confirmed registration of the cortical parcellation atlas to T1 images(Rorden et al. 2007).

Selection of Nodes

The Automated Anatomical Labeling Atlas(AAL) parcellates cortical and subcortical volumes into 90 regions(Tzourio-Mazoyer et al. 2002). The AAL is a macro-anatomical parcellation atlas based on a single subject brain template set in MNI space(Tzourio-Mazoyer et al. 2002). The AAL atlas applies spatial coordinates and associated volume for 90-120 cortical and subcortical

structures. Node definition excluded the cerebellum resulting in a 90 node parcellation scheme (45 nodes bilaterally).

Selection of Edges

Analysis of undirected and weighted edges included streamline count between nodes and mean fractional anisotropy(FA) between nodes. Averaged fractional anisotropy(FA) values between two nodes defined the FA edge weight(Levitt et al. 2012). To extend the previous DTI study that reported widespread FA reductions, we implemented FA edge weights in graph theory and sub-network analysis. Additionally, analysis of rich-club connections employed streamline count edge weights to examine effects of nodes rich in connections. Streamline count represents the total number of reconstructed streamlines interconnecting two nodes. Additionally, graph thresholding was applied to remove spurious streamlines, which when unaccounted for lead to unintended false-positives. Connection matrices were thresholded at a density value 0.2, which resulted in equivalent connection densities between groups but allowed connection weights to vary, minimizing false-positive streamline count(Fornito et al. 2012).

Network Metrics

The Brain Connectivity Toolbox contains the set of functions used to produce graph theory measures(Rubinov & Sporns 2010). Graph theory analysis implemented weighted undirected edge strengths across all analyses. Global and regional measures probe properties of integration and segregation(Rubinov & Sporns 2010; Bullmore & Sporns 2009; Bullmore & Sporns 2012). The metrics chosen for analysis in the study were (i) weighted degree: the number of connections attached through a node, (ii) weighted clustering coefficient: the ratio

of the sum of weights across all triangles around a node, (iii) weighted characteristic path length: measures the average shortest path length, i.e. the minimum number of edges that must be traversed to go from one node to another, (iv) weighted global efficiency: mathematically presented as the inverse of the shortest path length, (v) weighted local efficiency: the length of the shortest path between two nodes, containing only neighbors of the node of interest, and (vi) weighted betweenness centrality: describes nodes that participate in many short paths, reflecting a nodes influence in a network (Rubinov & Sporns 2010; Bullmore & Sporns 2009).

Nodal analyses were selected *a priori* from a previous DTI analysis in this cohort(Emsell, Langan, et al. 2013; Emsell, Leemans, et al. 2013). Nine bilateral nodes were selected(listed in Table 3) as endpoints of prefrontal white matter, cingulum, and callosal splenium connections(Emsell, Langan, et al. 2013).

Network Based Statistic

Collectively impaired interconnections or sub-networks investigated with the Network Based Statistic(NBS) toolbox characterize network differences by identification of particular inter-regional connections or components affected in one group of individuals relative to another. Studies investigating sub-networks in a number of brain disorders applied NBS analysis, however this technique has yet to be investigated in BD(Zalesky et al. 2010; Zalesky et al. 2012). The NBS identifies an experimental effect at the cluster level by performing mass univariate testing controlling for Family Wise Error(FWE) rate. First, statistical significance threshold was selected at $p<0.05$. Next, permutation testing performed 5000 permutations. The NBS requires selection of supra-threshold connections: as this threshold setting is quite arbitrary,

investigation across three supra-threshold values was employed, as has been most commonly implemented(Zalesky et al. 2010; Zalesky et al. 2012) . Finally, all connected components supra-threshold were compared between-groups(Zalesky et al. 2010).

Rich-club Coefficient

Next, we carried out an exploratory investigation of the "rich-club" coefficient among cortico-subcortical connections. The "rich-club" refers to a set of nodes that are rich in connections and densely inter-connected among themselves forming a club(McAuley et al. 2007; van den Heuvel & Sporns 2011). We investigated weighted rich-club connectivity differences between groups, as well as rich-club structural membership. The rich-club coefficient is defined by the following equation:

$$\phi\,(\mathrm{k}) = \frac{2E{>}k}{N{>}k(N{>}k-1)}$$

whereby, E>*k* indicates the weighted number of streamline connections greater than *k* present within a subgraph degree >*k*, as N>*k* indicates the number of nodes in the subgraph(McAuley et al. 2007; Collin et al. 2013). The measure ϕ reflects the level of interconnectivity between nodes. The rich-club identifies structural connections with a high value of *k*, removing all lower degree connections. The rich-club nodes will have a high *k* and high ϕ(McAuley et al. 2007; van den Heuvel & Sporns 2011; Collin et al. 2014).

Normalised Rich-club Coefficient

Normalized rich-club coefficient indicates that these densely interconnected structures were connected based on more than chance alone. A normalized coefficient is adjusted to a number

of comparable random networks by preserving the degree distribution(van den Heuvel & Sporns 2011). Normalized rich-club analysis uses a number of rewiring iterations of the preserved degree distribution to ensure effects are not due to chance. The weighted normalized rich-club coefficient is given by the following equation:

$$\phi w_{norm}(k) = \frac{\phi w(k)}{\phi w_{random}(k)}.$$

A weighted normalized rich-club coefficient $\Phi w_{norm}(k)$ was computed as the weighted rich club parameter $\Phi w(k)$ over a set of m=500 random networks of equal degree. As the sufficient number of rewirings lacks standardization with re-arrangements (m) ranging from 100 to 1000(Daianu et al. 2015; Kocher et al. 2015; van den Heuvel & Sporns 2011), selection of number of random rewirings(m=500) revealed a standard deviation(SD) that converges below .001. The number of appropriate rewiring iterations(m=500) was set at 10 to ensure normalization was met. By definition, Φw_{norm} >1 over a range of k implies the existence of a rich-club set(McAuley et al. 2007; van den Heuvel & Sporns 2011).

Rich-Club Membership

Validation methods confirmed rich-club membership. Rich-club members defined at the statistical significant network between patients and controls(k=56) displayed approximately 10-12 highly connected nodes. We identified rich-club members at Φw_{norm}>1 across range k at a group threshold 60% and 70% of participants to determine rich-club structures most consistent across individual networks. Additionally, top 10 highest weighted degree nodes confirmed rich-club members were not dependent on one hub definition alone.

Statistics

Statistical analysis of global and regional metrics (degree, clustering coefficient, betweenness centrality, characteristic path length, global efficiency and local efficiency) applied MANCOVA tests, co-varied for age and gender, using IBM SPSS statistics software version 22(IBM SPSS Amos 2012). Calculations of global values from nodal measures averaged values across all 90 nodes to generate a global average for each measure. We corrected for global connectivity to assess whether findings were indicative of reduced connectivity globally or potentially affected topological organization. Global analyses and regional comparisons underwent False Discovery Rate(FDR) correction for multiple comparisons(Benjamini & Hochberg 1995).

Permutation testing was used to assess between group effects in rich club connectivity. We performed 9999 Monte Carlo resamples using R software(RStudio 2012). Multiple comparisons corrected for 28 possible values of *k* density was implemented using the FDR method(Benjamini & Hochberg 1995).

We applied partial correlations co-varying for age and gender to assess the relationship between clinical symptoms scales, illness duration and lithium use, and significant graph theory metrics. Global efficiency was correlated with rich-club density co-varying for age and gender to determine a possible relationship between global integration and hub inter-connectivity.

Results

The socio-demographic and clinical details of the participants are outlined in Table 1. Participants and healthy volunteers were age and gender matched. On average, patients indicated a lower number years of education than healthy volunteers. The mean age of onset of

illness in patients was 28 years of age. Thirty-three of the patients took mood stabilizers at the time of scanning with most using lithium (29); twenty-two patients took antipsychotic, most used olanzapine (15); and eight patients used antidepressants. Four participants in the BD group were unmedicated at time of MRI scan.

Global and Regional Graph Theory Metrics:

Analysis of global properties revealed statistically significant group differences whereby the BD group displayed increased characteristic path length and reduced global efficiency and clustering coefficient compared with the healthy volunteer group when connections were weighted by FA[Table 2; Figure 1]. Seven of the regions connected by fronto-limbic and parieto-occipital pathways revealed significant connectivity differences surviving multiple comparison correction. In BD, reduced clustering and local efficiency predominantly incorporated the superior and middle frontal nodes and superior and middle occipital nodes, when defined by FA[Table 3]. Findings did not change when corrected for global connectivity, defined by the global density metric. Preserved measures of degree and density indicate significant differences in topology may be the primary feature of bipolar disorder.

Network Based Statistic:

The BD group displayed significantly weaker sub-network connectivity, with a single disconnected sub-network identified for each threshold (2, 2.5, 3). The NBS provides two outputs a) the supra-threshold set of connections comprised in the graph component found to show a significant effect as well as b) a corresponding p-value for each such network(Zalesky et al. 2010)[Figure 2]. We identified collective network dysconnectivity differences with supra-threshold connections (t=2[p=0.015]), consisting of frontal, parietal and occipital connections in

BD. Higher supra-threshold connections (t=2.5[p=0.017] and t=3[p=0.020]) revealed structural dysconnectivity among parietal and occipital connections in patients compared to healthy controls.

Rich-Club Connectivity:

In this analysis, weighted rich-club connection density ranged from 27-64, while normalized rich-club coefficient ranged from 28-56. Normalized rich-club connectivity effects demonstrate statistical significance before FDR multiple comparison correction across two possible connection densities (*k*=55, Z=-2.236, p=0.024; *k*=56, Z=-2.654, p=0.0067). After FDR correction for 28 possible densities, *k*=56 demonstrated a moderate to large effect size (Cohen's d=0.59).

Rich-Club Membership:

Following examination of rich-club connectivity effects, we investigated rich-club membership. Rich-club structures were selected by the group-averaged cortico-subcortical network for the statistically significant $\Phi w_{norm}(k)$ and identified nodes connected by this pathway. Rich-club connections shared by 60% of participants indicate differential hub participation between groups. Although we identified rich-club members connected by pathways at 60% group threshold, we applied a more stringent threshold of 70% to identify what findings were consistent. Previously, pathways present in >50% of participants were taken into account(van den Heuvel & Sporns 2011). Additionally, the top 10 highest degree nodes were identified to validate the threshold selection(Collin et al. 2014; van den Heuvel & Sporns 2011).

Rich-club members revealed the following hubs: superior frontal gyrus, middle cingulate gyrus, hippocampus, caudate, precuneus and thalamus[Figure 3]. In BD rich-club membership at group threshold 60% indicated the right frontal superior gyrus and right middle cingulate gyrus

were not included in the rich-club in most BD patients; however, BD rich-club structures incorporate the left middle occipital gyrus. Of interest, when we assessed rich-club membership in 70% of participants, the most notable between-group differences in the BD group supported the absence of the right superior frontal gyrus and left thalamus as hubs, and additionally the left middle occipital gyrus was no longer integrated in patients(Figure 3). Of note, dysconnections identified by the network based statistics analysis overlap with rich-club members, namely left hippocampus, precuneus and thalamus.

Clinical Correlates

Partial correlations show rich-club connectivity is associated with global efficiency in all participants($r=.299$, $p<0.006$)[Figure 4]. Taken together, the normalized rich-club coefficient revealed trend connectivity effects as well as rich-club membership differences. Global efficiency appears to be related to rich-club connectivity, supporting the role of rich-club connections in global integration.

Partial correlations did not reveal any significant association between graph theory properties and clinical measures including: age of onset, illness duration, whether patients were taking lithium at time of scan, as well as years of medication use.

Discussion

This study provides novel evidence of distributed neuroanatomical dysconnectivity, using graph theory metrics, as a trait based feature of BD. We found reductions in global and regional efficiency in patients compared to controls indicating abnormal connectivity patterns in BD. Specifically, longer characteristic path length, reduced global efficiency, and lower mean clustering coefficient are indicative of widespread anatomical dysconnectivity. This analysis is consistent with three studies which identified reduced global efficiency in bipolar disorder (Leow et al. 2013; Gadelkarim et al. 2014; Collin et al. 2015). However, two other studies determined connectivity to be preserved globally(Forde et al. 2015; Wheeler et al. 2015). In contrast to the present analysis which used volumetric parcellation, one study used cortical thickness to define nodes and did not demonstrate differences in connection density between healthy individuals and BD in a multi-center study(Wheeler et al. 2015). Impaired global integration may be a general pathophysiological feature across brain disorders(Crossley et al. 2014; Fornito et al. 2015); therefore regional connectivity may elucidate topological patterns involved in emotional dysregulation and its effect on whole-brain integration.

Uncorrected regional analyses of clustering and local efficiency identified widespread reductions among fronto-limbic, parietal and occipital connections, consistent with previous studies(Gadelkarim et al. 2014; Leow et al. 2013; Forde et al. 2015). Furthermore, regional dysconnectivity of the left middle frontal gyrus and right superior medial frontal gyrus has been supported in a recent investigation in patients from families multiply affected with BD(Forde et al. 2015). Similarly, the present dataset demonstrates callosal dysconnectivity due to regional frontal patterns of disorganization. Additionally, parietal and default mode network

dysconnectivity identified by regional and network based analysis is corroborated by an investigation of path length associated community estimation(Gadelkarim et al. 2014).This analysis indicates connectivity abnormalities in BD appear to extend beyond fronto-limbic regions to other association areas of the brain(Nortje et al. 2013; Vederine et al. 2011; Wise et al. 2015). These reductions may be related to features of topological dysconnectivity as opposed to reduced connectivity globally, as findings are unchanged when corrected for global connectivity.

Furthermore, the network-based statistic measure identified a collection of interconnections encompassing fronto-limbic and parietal/occipital connections(Gadelkarim et al. 2014). Moreover, weaker connectivity of network components in patients indicates these impaired connections interact collectively supporting BD as a dysconnection syndrome(O'Donoghue et al. 2015). Analysis of highest supra-threshold connections revealed dysconnectivity among the cuneus, precuneus, and superior occipital connections. Interestingly, evidence from functional connectivity analyses support a model of affected posterior default mode network as well as parieto-occipital dysconnectivity(Strakowski et al. 2011; Strakowski et al. 2005). Strakowski proposed that self-referential thinking and interpretation of visual stimuli is affected in disturbances of this network, namely altered functional connectivity of the precuneus and cuneus(Strakowski et al. 2000; Strakowski et al. 2002). These structures are topologically central with high degree, which may be particularly affected in BD(Crossley et al. 2014; Gadelkarim et al. 2014).

Investigation of rich-club connectivity effects shows trend-level reductions in BD. The associated relationship between global efficiency and rich-club density suggest widespread

neuroanatomical dysconnectivity may be related to communication among these central structures(Crossley et al. 2014; van den Heuvel et al. 2013). Recent studies report reduced rich-club connectivity in schizophrenia and unaffected siblings with schizophrenia(van den Heuvel et al. 2013; Collin et al. 2015; Collin et al. 2014). In BD, one study to date reports preserved rich-club connections (Collin et al. 2015). Results of the present cortico-subcortical rich-club connectivity analysis are in contrast to this study which was confined to cortico-cortical connections(Collin et al. 2015). The significance of the limbic system in BD argues for the inclusion of sub-cortical limbic structures in network mapping. Differences in subcortical volume in BD has a substantial body of literature to support its role in the aetiology and as a trait feature of the illness(Quigley et al. 2015; Houenou et al. 2012; Strakowski et al. 2012; Vargas et al. 2013; van Erp et al. 2015; Hibar et al. 2016). Additionally, during tract reconstruction we implemented constrained spherical deconvolution to overcome the challenges of white matter reconstruction in sub-cortical areas.

Next, we address the consistency in rich-club structures and hubs affected in BD. Therefore, this investigation examined regions connected by the statistically significant pathway and detected hub involvement specific to BD. The investigation by Collin and colleagues(Collin et al. 2015) examined additional rich-club classifications using the top 20% betweenness-centrality nodes and top 10% highest degree nodes. These hubs consisted of portions of bilateral cingulate, precuneus, superior frontal, parietal and temporal gyri, as well as pre and post central gyri and insular cortices(Collin et al. 2015). In the present study, we defined hubs connecting pathways present in most participants and validated by top 10% highest degree nodes, which confirmed these rich-club structures. Cingulate, precuneus and superior frontal structures appear to be

consistent across investigations and hub definitions, potentially due to above average connectivity and participation across both cortical and cortico-subcortical mappings(van den Heuvel et al. 2013; Collin et al. 2014; Collin et al. 2015). Additionally, rich-club members in this analysis were identified as hubs in a study of patients with schizophrenia, defined by betweenness centrality, when network analysis implemented the equivalent structural atlas(van den Heuvel et al. 2010). Validation of this parcellation scheme merits reproducibility of these structures as critical hubs in cortico-subcortical networks.

In the current study, the superior frontal gyrus was absent from the bipolar group rich-club, suggesting differential involvement of this densely interconnected frontal structure. Hub deficits reported in the study of patients with schizophrenia support rich-club members affected in the current analysis; consistent with a less central role of frontal hubs in psychotic illnesses(van den Heuvel et al. 2010). This absence was maintained when the rich-club pathway was defined among group thresholds 60% of patients and 70% of patients. Nodes anatomically connected with the superior frontal gyrus, also present in the rich-club network, include the caudate and thalamus(Li et al. 2013; Haznedar et al. 2005). These deficits are consistent with a DTI study reporting reduced FA in the anterior thalamic radiation in both BD and schizophrenia patients(Sussmann et al. 2009). While thalamic function has been implicated previously in BD, volumetric analyses of the thalamus have been varied(Hallahan et al. 2011). Rich-club members presented in the 60% group threshold indicated above average connectivity of the right middle cingulate gyrus in healthy controls, absent in the BD group. Moreover, the BD group rich-club additionally involves the left middle occipital gyrus, which may potentially represent a compensatory effect from disrupted frontal connectivity(Griffa et al. 2013). Differential

involvement of rich-club structures and reduced connection density between these rich-club structures may well contribute to the global connectivity effects identified in this study. Inter-hemispheric dysconnectivity was not specifically examined in this investigation, where it has been supported as a feature of BD in previous structural network studies(Leow et al. 2013; Caeyenberghs & Leemans 2014; Gadelkarim et al. 2014; Collin et al. 2015).

Methodological selections must be considered when interpreting these network findings(Fornito, Zalesky, et al. 2013; de Reus & van den Heuvel 2013). As network analyses lack standardized recommendations and methodological criteria at this point; this network reconstruction carries challenges when interpreting and reconciling results across investigations(Fornito, Zalesky, et al. 2013). Methodological considerations in this novel and evolving field include the specific choice of parameters for white matter tract reconstruction, edge weights of fractional anisotropy measures and streamline count. Advancing from previous research by use of more biologically relevant connection weights as well as a template cortical parcellation may identify less variable effects(Fornito, Zalesky, et al. 2013). Extension of this work would improve from a subject-specific parcellation technique integrated in network analysis reliably. The field would benefit from some degree of standardization in these approaches, which would assist in directly comparing results as they emerge from research groups.

A strength of the current analysis is the parcellation scheme employed in the brain mapping pipeline. A majority of complex network analyses limit their connectome maps to cortical connection maps, while this analysis extended to cortico-subcortical mapping. The scale at which the brain should be accurately mapped to be most biological meaningful is not yet

standardized(Fornito, Zalesky, et al. 2013). Additionally, we attempt to explain hub participation differences in BD through examination of rich-club membership.

Taken together, these analytical methods support previous DTI investigations, and extend further understanding of structural dysconnectivity in BD. The relationship of graph measures to pathophysiological mechanisms is an active area of examination(Fornito, Zalesky, et al. 2013). The relevance of this study indicates dysconnectivity to be a pathophysiologically relevant trait related feature of BD, with differentially affected rich-club structures being particularly informative to describe complex structural integration.

Conclusion

This multifaceted analysis employing graph theory metrics provides substantial additional evidence for anatomical dysconnectivity representing a trait feature of BD. This study supports reductions in global efficiency and local connectedness of limbic structures, and extends initial investigations of BD sub-networks, identifying weaker connected components incorporating anterior and posterior brain networks representing trait features of BD.

Financial Disclosures: The research of A.L. is supported by VIDI Grant 639.072.411 from the Netherlands Organisation for Scientific Research (NWO). B. J. is a postdoctoral fellow supported by the Research Foundation Flanders (FWO Vlaanderen). GJB receives honoraria for teaching from General Electric Healthcare, and acts as a consultant for IXICO.

Conflict of interest: None

Acknowledgments & Funding: This research was supported by the Hardiman Research Scholarship, National University of Ireland, Galway, Galway Ireland and the Health Research Board (HRB) (HRA_POR/2011/100). We gratefully acknowledge the participants of this study and the radiographers of the University Hospital Galway Magnetic Resonance Imaging Department for their support during data collection.

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Table 1. Clinical and Demographic Variables

	Healthy Controls	Bipolar Group	Statistical Comparison (Test Statistic, p)
Number of Subjects	43	42	
Age, Years, mean ± SD	40.3 ± 9.5	39.3 ± 10.3	t= 1.497, p=0.138
Gender, male/female, n	20/22	23/19	χ^2=.110, p=0.740
Education, Years, mean ± SD	17.9 ± 2.9	15.4 ± 3.6	t= 3.329, p<0.001
Age of Onset, years, mean ± SD	-	28.7 ± 7.9	
Illness Duration, years, mean ± SD	-	10.9 ± 8.8	
Number of Hospitalizations, mean ± SD	-	1.5 ± 1	
Hamilton Depression Rating Scale (HDRS), mean ± SD, [range]	-	.9 ± 1.4 [0-7]	
Young Mania Rating Scale (YMRS), mean ± SD, [range]	-	.45 ± 1 [0-4]	
Global Assessment of Functioning (GAF), mean ± SD	-	84.5 ± 5.3	

Table 1 Legend. Participants were age and gender matched. Years of education differed between groups. All participants in the bipolar group were confirmed prospectively euthymic with clinical rating scales of mania and depression less than a score of 7.

Table 2. Global Graph Theory Measures

Metric	HC (Mean ± SD)	BD (Mean ± SD)	F, p value
Betweenness Centrality	64.75 ± 5.52	64.52 ± 6.93	0.060, 0.807
Clustering Coefficient	0.23 ± 0.01	0.22 ± 0.02	4.083, 0.047*
Characteristic Path Length	4.10 ± 0.16	4.21 ±0.26	5.975, 0.017*
Degree	45.49 ± 2.45	45.27 ± 2.38	0.021, 0.885
Global Efficiency	0.27 ± 0.01	0.26 ± 0.02	6.137, 0.015*

Table 2 Legend. * Indicates significant p-value after multiple comparison correction. GLM model was applied, ANCOVA was carried out across global measures. Three of five global measures were deemed significant following at $p<0.05$.

Table 3. Regional Connectivity Differences between Patients and Controls

Nodes		Clustering Coefficient F [p value]	Local Efficiency F [p value]
Precentral Gyrus	Left	2.641 [0.108]	3.415 [0.068]
	Right	5.078 [0.027]	7.819 [0.006]
Superior Frontal Gyrus	Left	6.575 [0.012]	9.411 [0.003*]
	Right	0.049 [0.825]	4.147 [0.045]
Middle Frontal Gyrus	Left	5.464 [0.022]	10.937 [0.001*]
	Right	3.174 [0.079]	8.271 [0.005*]
Medial Superior Frontal Gyrus	Left	6.422 [0.013]	5.042 [0.027]
	Right	4.323 [0.041]	5.499 [0.021]
Anterior Cingulate Gyrus	Left	6.402 [0.013]	4.897 [0.030]
	Right	4.978 [0.028]	4.30 [0.040]
Middle Cingulate Gyrus	Left	0.654 [0.421]	2.415 [0.124]
	Right	1.818 [0.181]	5.084 [0.027]
Superior Parietal Gyrus	Left	2.955 [0.089]	3.400 [0.069]
	Right	5.258 [0.024]	3.786 [0.055]
Superior Occipital Gyrus	Left	15.371 [0.000*]	12.913 [0.001*]
	Right	6.929 [0.010]	9.870 [0.002*]
Middle Occipital Gyrus	Left	6.185 [0.015]	8.527 [0.005*]
	Right	4.669 [0.034]	5.097 [0.027]

Table 3. This analysis examined two different local graph measures in FA connections. MANCOVAs were carried out between groups, co-varying for age and gender. * indicates significant p-value after FDR correction. Nine nodes bilaterally were selected a priori from a previous data driven DTI analysis(Emsell, Leemans, et al. 2013; Emsell, Langan, et al. 2013) for analyses of local graph theory measures.